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(57) Abstract

Substituted heteroaromatic compounds, in particular substituted tricyclic fused compounds in which one terminal ring is pyridine or pyrimidine, are protein tyrosine kinase inhibitors. The compounds are described as are methods for their preparation, pharmaceutical compositions including such compounds and their use in medicine, for example in the treatment of psoriasis, fibrosis, atherosclerosis, restenosis, auto-immune disease, allergy, asthma, transplantation rejection, inflammation, thrombosis, nervous system diseases, and cancer.

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# TRICYCLIC FUSED COMPOUNDS AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

The present invention relates to a series of substituted heteroaromatic compounds, methods for their preparation, pharmaceutical compositions containing them and their use in medicine. In particular, the invention relates to tricyclic fused systems containing a pyridine or pyrimidine ring which exhibit protein tyrosine kinase inhibition.

Protein tyrosine kinases catalyse the phosphorylation of specific tyrosyl residues in various proteins involved in the regulation of cell growth and differentiation (A.F.Wilks, Progress in Growth Factor Research, 1990 (2), 97-111). Protein tyrosine kinases can be broadly classified as growth factor receptor (e.g. EGF-R, PDGF-R, FGF-R and c-erbB-2) or non-receptor (e.g. c-src, bcr-abl) kinases. Inappropriate or uncontrolled activation of many of these kinases i.e. aberrant protein tyrosine kinase activity, for example by over-expression or mutation, has been shown to result in uncontrolled cell growth.

Aberrant activity of protein tyrosine kinases such as c-erbB-2, c-src, EGF-R and PDGF-R has been implicated in human malignancies.

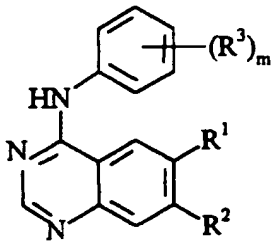
Aberrant EGF-R activity has, for example, been implicated in cancers of the head and neck, and aberrant c-erbB-2 activity in breast, ovarian, non-small cell lung, pancreatic, gastric and colon cancers. Inhibitors of protein tyrosine kinase should therefore provide a treatment for tumours such as those outlined above.

Aberrant protein tyrosine kinase activity has also been implicated in a variety of other disorders: psoriasis, (Dvir et al, J.Cell.Biol; 1991, 113, 857-865), fibrosis, atherosclerosis, restenosis, (Buchdunger et al, Proc.Natl.Acad.Sci. USA; 1991, 92, 2258-2262), auto-immune disease, allergy, asthma, transplantation rejection (Klausner and Samelson, Cell; 1991, 64, 875-878), inflammation (Berkois, Blood; 1992, 79(9), 2446-2454), thrombosis (Salari et al, FEBS; 1990, 263(1), 104-108) and nervous system diseases (Ohmichi et al, Biochemistry, 1992, 31, 4034-4039). Inhibitors of the specific protein tyrosine kinases involved in these diseases eg PDGF-R in restenosis and EGF-R in psoriasis, should lead to novel therapies for such disorders. P56lck and zap 70 are indicated in disease

conditions in which T cells are hyperactive eg rheumatoid arthritis, autoimmune disease, allergy, asthma and graft rejection.

Published European Patent number 0635507 discloses tricyclic quinazoline derivatives and their preparation for use in the treatment of cancer. This citation notes that receptor tyrosine kinases in general, which are important in the transmission of biochemical signals initiating cell replication, are frequently present in common human cancers such as breast cancer (Sainsbury *et al* Brit. J. Cancer 1988, 58, 458). This citation also states that tyrosine kinase activity is rarely detected in normal cells whereas it is frequently detectable in malignant cells (Hunter, Cell, 1987, 50, 823) and it is suggested that inhibitors of receptor tyrosine kinase should be of value as inhibitors of the growth of mammalian cancer cells (Yaish *et al*. Science, 1988, 242, 933). This citation has the aim of providing quinazoline derivatives which inhibit receptor tyrosine kinases involved in controlling the tumourigenic phenotype.

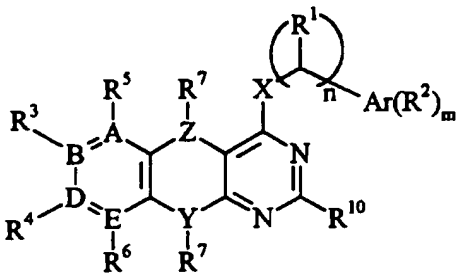
The tricyclic derivatives of EP0635507 are of the formula (1) :



(1)

wherein $R^1$ and $R^2$ together form specified optionally substituted groups containing at least one heteroatom so as to form a 5 or 6 membered ring, optionally substituted by one or two specified substituents, in which a N atom is located at the 6-position of the quinazoline ring. $R^3$ includes, independently, hydrogen, hydroxy, halogeno, (1-4C)alkyl, (1-4C) alkoxy, di-[(1-4C)alkyl]amino, or (2-4C)alkanoylamino. There is, however, no mention of substitution of the 4-anilino ring by a further group contining an aromatic or heterocyclic moiety.

WO95/19970 discloses tricyclic compounds of formula (2) which are capable of inhibiting EGF-R tyrosine kinase:

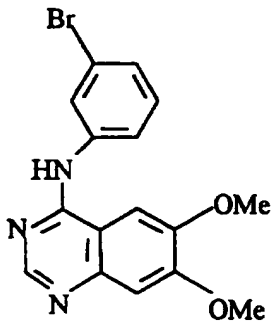


(2)

in which Y and Z are:
(i) both C, both N or one is N and the other is C, or
(ii) one of Y or Z is C=C or C=N and the other represents a bond, or
(iii) one of Y or Z is N, O or S and the other is a bond; and
A, B, D and E can be all C; or two of them may be N provided the remainder are C, or any two contiguous positions in A-E may be a single heteroatom N, O or S provided that at least one of the remaining atoms is C; and X is O, NR or S. $R^2$ includes lower alkyl, lower alkoxy, cycloalkyl and cycloalkoxy, or two $R^2$ may together form a 5-7 membered carbocyclic ring. There is, however, no suggestion that the aromatic ring (Ar) may be substituted by a further group containing an aromatic or heterocyclic moiety.

However, broad spectrum inhibition of protein tyrosine kinase may not provide optimal treatment of the tumour, and could in certain cases even be deterimental to subjects since protein tyrosine kinases provide an essential role in the normal regulation of cell growth.

Selective inhibition of the EGF receptor is, however, disclosed by Fry et al (Science, 265, 1093 (1994)). This citation discloses that the compound of formula:



is a highly selective inhibitor of the EGF receptor tyrosine kinase at picomolar concentrations while inhibiting other tyrosine kinases only at micromolar or higher concentrations. However, there is no reference to any tricyclic compounds in this citation.

It is therefore a general object of the present invention to provide compounds suitable for the treatment of disorders mediated by protein tyrosine kinase activity, and in particular treatment of the above mentioned disorders. In addition to the treatment of tumours, the present invention envisages that other disorders mediated by protein tyrosine kinase activity may be treated effectively by preferential inhibition of the appropriate protein tyrosine kinase activity.

It is another object of the present invention to provide compounds which preferentially inhibit protein tyrosine kinases, such as c-erbB-2, c-src, p56lck, EGF-R, PDGF-R, and zap70 protein tyrosine kinases.

A further object of the present invention is to provide compounds useful in the treatment of protein tyrosine kinase related diseases which minimise undesirable side-effects in the recipient.

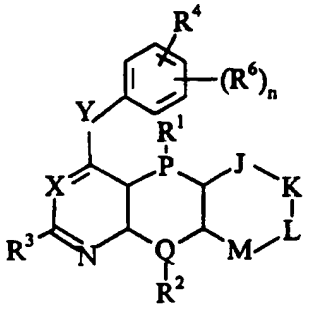
The present invention relates to certain tricyclic pyridine and pyrimidine derivatives which may be used to treat disorders mediated by protein tyrosine kinases and in particular have anti-cancer properties. More particularly, the compounds of the present invention are potent inhibitors of protein tyrosine kinases such as c-erbB-2, EGF-R and p56lck thereby allowing clinical management of particular diseased tissues.

The present invention envisages, in particular, the treatment of human malignancies, for example breast, stomach, ovary, colon, lung and pancreatic tumours, especially those driven by c-erbB-2, using the compounds of the present invention. For example, the invention includes compounds which are highly active against the c-erbB-2 protein tyrosine kinase in preference to the EGF receptor kinase hence allowing treatment of c-erbB-2 driven tumours.

More particularly, the present invention envisages that disorders mediated by protein tyrosine kinase activity may be treated effectively by inhibition of the

appropriate protein tyrosine kinase activity in a relatively selective manner, thereby minimising potential side effects.

Accordingly, the present invention provides a compound of formula (I):



(I

or a pharmaceutically acceptable salt thereof, wherein:

J, K, L, and M form a saturated or unsaturated fused ring which is optionally substituted and in which:

(i) each of J, K, L and M represent carbon atoms that may be independently replaced by N, O or S; or

(ii) any two contiguous positions in J, K, L and M taken together represent a single atom C, N, O or S with at least one of the remaining atoms being carbon and the other being selected from carbon, N, O or S; or

(iii) any two contiguous positions in J, K , L and M taken together represent a N atom with the remaining atoms also being N;

so that when the fused 5 or 6-membered ring represented by J, K, L and M bears one or two optional substituents in order to satisfy the valency requirements of the atoms in the fused ring and:

(i) when the ring atom is carbon, the substituents are independently selected from the group comprising: amino, cyano, halogen, hydroxy, $C_{1-4}$ alkyl, $C_{1-4}$ alkoxy, $C_{1-4}$alkylthio, $C_{1-4}$ alkylsulphinyl, $C_{1-4}$ alkylamino, or

(ii) when there are two adjacent carbon atoms in the fused ring, two substituents together form an optionally substituted methylenedioxy or ethylenedioxy group, or

(iii) when the ring atom is nitrogen, the substituents are independently selected from the group comprising: $C_{1-4}$ alkyl, amino $C_{2-4}$ alkyl, hydroxy $C_{2-4}$ alkyl and $C_{1-4}$ alkoxy $C_{2-4}$ alkyl;

subject to the provisos in (i) and (ii) above that the skeleton of the fused heterocyclic ring does not contain more than two atoms selected from O and S, and where the fused ring contains two such atoms said atoms do not occupy adjacent positions in the fused ring;

P and Q are carbon atoms in an aromatic ring which may be independently replaced by O, N, S, or a bond, or one of P and Q is C=C or C=N and the other a bond;

X is N or CH;

Y is a group $W(CH_2)$, $(CH_2)W$, or W, in which W is O, $S(O)_m$ wherein m is 0, 1 or 2, or $NR^a$ wherein $R^a$ is hydrogen or a $C_{1-8}$ alkyl group;

$R^1$ and $R^2$ are independently selected as appropriate to the nature of P and Q from the group comprising: not present, a lone pair of electrons, amino, hydrogen, halogen, hydroxy, nitro, carboxy, trifluoromethyl, trifluoromethoxy, carbamoyl, ureido, $C_{1-8}$ alkyl, $C_{1-8}$ alkoxy, $C_{3-8}$ cycloalkoxy, $C_{4-8}$ alkylcycloalkoxy, $C_{1-8}$ alkoxycarbonyl, N-$C_{1-4}$ alkylcarbamoyl, N,N-di-[$C_{1-4}$ alkyl]carbamoyl, hydroxyamino, $C_{1-4}$ alkoxyamino, $C_{2-4}$ alkanoyloxyamino, $C_{1-4}$ alkylamino, di[$C_{1-4}$ alkyl]amino, $C_{1-8}$ alkylthio, arylthio, $C_{1-4}$ alkylsulphinyl, arylsulphinyl, $C_{1-4}$ alkylsulphonyl, arylsulphonyl, halogeno-$C_{1-4}$ alkyl, and hydroxy-$C_{1-4}$ alkyl;

$R^3$ is selected from the group comprising; hydrogen, halogen, trifluoromethyl, $C_{1-4}$ alkyl and $C_{1-4}$ alkoxy;

$R^4$ is a group $ZR^5$ wherein Z is joined to $R^5$ through a $(CH_2)p$ group in which p is 0, 1 or 2 and Z represents a group $V(CH_2)$, $V(CF_2)$, $(CH_2)V$, $(CF_2)V$, or V in which V is a hydrocarbyl group containing 0,1 or 2 carbon atoms, carbonyl, CH(OH), sulphonamide, amide, O, $S(O)_m$ or $NR^b$ where $R^b$ is hydrogen or $R^b$ is $C_{1-4}$ alkyl;

or $R^4$ is a group $ZR^5$ in which Z is $NR^b$, and $NR^b$ and $R^5$ together form an optionally substituted 5, 6, 7, 8, 9 or 10-membered heterocyclic moiety;

$R^5$ is an optionally substituted 5, 6, 7, 8, 9 or 10-membered carbocyclic or heterocyclic moiety, or an optionally substituted $C_{3-6}$ cycloalkyl provided p is not zero; and

each $R^6$ is independently selected from the group comprising; hydrogen, hydroxy, halogen, $C_{1-4}$ alkyl, $C_{1-4}$ alkoxy, $C_{1-4}$ alkylamino, di-[$C_{1-4}$ alkyl]amino, $C_{1-4}$ alkylthio, $C_{1-4}$ alkylsulphinyl, $C_{1-4}$ alkylsulphonyl, $C_{1-4}$ alkylcarbonyl, $C_{1-4}$ alkylcarbamoyl, di-[$C_{1-4}$ alkyl] carbamoyl, carbamyl, $C_{1-4}$ alkoxycarbonyl, cyano, nitro and trifluoromethyl, and n is 1,2 or 3.

In an embodiment, P and Q are both C atoms, and in a preferred aspect J, K, L, and M are all C atoms, and more preferably with J, K, L and M forming a further aromatic ring.

In another embodiment, one of P and Q is a N, O or S atom, with the other being a bond. In a preferred aspect, J, K, L and M are all C atoms, more preferably with J, K , L and M forming a further aromatic ring.

In an embodiment, $R^1$ and $R^2$ are independently selected from the group comprising: amino, hydrogen, halogen, hydroxy, nitro, $C_{1-8}$ alkyl, $C_{1-8}$ alkoxy, $C_{1-8}$ alkylthio, $C_{1-8}$ alkylsulphinyl, $C_{1-8}$ alkylsulphonyl, and $C_{1-4}$ alkylamino;
$R^3$ is hydrogen, $C_{1-4}$ alkyl, $C_{1-4}$ alkoxy or halogen;
$R^5$ is an optionally substituted 5, 6, 7, 8, 9 or 10 membered-carbocyclic or heterocyclic moiety;
$R^6$ is hydrogen, hydroxy, halogen, $C_{1-4}$ alkyl, $C_{1-4}$ alkoxy, di-[$C_{1-4}$ alkyl]amino, nitro or trifluoromethyl; and
Z is oxygen, S or $NR^b$ wherein $R^b$ is hydrogen, or $C_{1-4}$ alkyl.

In a further embodiment, $R^1$ and $R^2$ are independently selected from the group comprising: hydroxy, halogen, amino, $C_{1-4}$ alkyl such as methyl, and $C_{1-4}$ alkoxy such as methoxy.

In a further embodiment, $R^3$ is hydrogen or methyl; preferably $R^3$ is hydrogen.

In a further embodiment, $R^4$ is selected from the group comprising: benzyl, phenoxy and benzyloxy; and in a preferred aspect, X is N and Y is NH; or X is CH and Y is O, $S(O)_m$ wherein m and $R^a$ are as herein before defined.

In a further embodiment, $R^4$ is in the para position with respect to Y.
In a further embodiment, $R^5$ is thiophene or cyclohexane and p is 1 where Z is oxygen
In a further embodiment $R^6$ is hydrogen, halogen or methyl, preferably $R^6$ is hydrogen.

In a further embodiment, $(R^6)_n$ represents meta substituent(s) with respect to Y, preferably n = 1.

In a further embodiment, X is N.

In a further embodiment, Y is $NR^b$, $NR^b(CH_2)$, or $(CH_2)NR^b$, preferably Y is $NR^b$ wherein R is hydrogen or methyl, preferably R is hydrogen.

In a further embodiment, Z is $CH_2$, $NR^b$, $NR^b(CH_2)$, $(CH_2)NR^b$,O, $O(CH_2)$, $O(CF_2)$, $(CH_2)O$, $(CF_2)O$, $S(CH_2)$, or carbonyl; preferably Z is $CH_2$, $NR^b$, O, $O(CH_2)$ or $O(CF_2)$, and more preferably Z is O.

Preferred compounds of the present invention include:
4-(4-Benzyloxyanilino)benzo[g]quinazoline hydrochloride and
4-(4-Benzyloxyanilino)benzothieno[3,2-d]pyrimidine hydrochloride.

The fused 5 or 6-membered ring represented by J, K, L and M may optionally bear one or two substituents in order to satisfy the valency requirements of the atoms in the fused ring. Where the ring atom is carbon suitable substituents include: amino, cyano, halogen, hydroxy, $C_{1-4}$ alkyl, $C_{1-4}$ alkoxy, $C_{1-4}$alkylthio, $C_{1-4}$ alkylsulphinyl, $C_{1-4}$ alkylamino. Where there are two adjacent carbon atoms in the fused ring, two substituents together may form an optionally substituted methylenedioxy or ethylenedioxy group. Suitable substituents for a nitrogen atom in the fused ring include: $C_{1-4}$ alkyl, amino $C_{1-4}$ alkyl, hydroxy $C_{1-4}$ alkyl and $C_{1-4}$ alkoxy $C_{1-4}$ alkyl.

Suitably the 5, 6, 7, 8, 9 or 10- membered heterocyclic moiety is selected from the group comprising: furan, dioxolane, thiophene, pyrrole, imidazole, pyrrolidine, pyran, pyridine, pyrimidine, morpholine, piperidine, oxazoline, oxazolidine, thiazole, thiadiazole, benzofuran, indole, isoindole, quinazoline, quinoline and isoquinoline.

Suitably the 5, 6, 7, 8, 9 or 10- membered carbocyclic moiety is selected from the group comprising: phenyl, benzyl, indene, napthalene, tetralin, decalin, cyclopentyl, cyclohexyl, and cycloheptyl.

By halo is meant fluoro, chloro, bromo or iodo.

Alkyl groups containing three or more carbon atoms may be straight, branched or cyclised.

Heterocyclic groups comprise one or more rings which may be saturated, unsaturated, or aromatic and which may independently contain one or more heteroatoms in each ring.

Carbocyclic groups comprise one or more rings which may be independently saturated, unsaturated or aromatic and which contain only carbon and hydrogen.

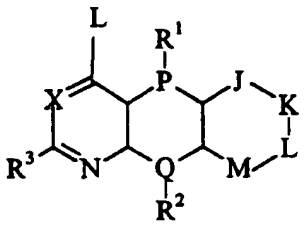
Optional substituents include, but are not limited to, hydroxy, halogen, trifluoromethyl, trifluoromethoxy, nitro, amino, cyano, $C_{1-4}$ alkoxy, $C_{1-4}$ alkylthio, $C_{1-4}$ alkyl carbonyl, carboxylate, $C_{1-4}$ alkoxy carbonyl, carboxamide, $C_{1-4}$ alkylamino carbonyl and di[$C_{1-4}$ alkyl]amino.

Certain compounds of the formula (I) contain asymmetric carbon atoms and are, therefore, capable of existing as optical isomers. The individual isomers and mixtures of these are included within the scope of the present invention. Likewise, it is understood that compounds of formula (I) may exist in tautomeric forms other than that shown in the formula.

Salts of the compounds of the present invention may comprise acid addition salts derived from a nitrogen in the compound of formula (I). The therapeutic activity

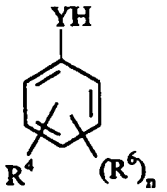
resides in the moiety derived from the compound of the invention as defined herein and the identity of the other component is of less importance although for therapeutic and prophylactic purposes it is, preferably, pharmaceutically acceptable to the patient. Examples of pharmaceutically acceptable acid addition salts include those derived from mineral acids, such as hydrochloric, hydrobromic, phosphoric, metaphosphoric, nitric and sulphuric acids, and organic acids, such as tartaric, acetic, trifluoroacetic, citric, malic, lactic, fumaric, benzoic, glycollic, gluconic, succinic and methanesulphonic and arylsulphonic, for example p-toluenesulphonic, acids.

In a further aspect, the present invention provides a process for the preparation of a compound of the formula (I), or a pharmaceutically acceptable salt thereof, which process comprises the reaction of a compound of the formula (II).



(II)

with a compound of the formula III :



(III)

wherein L is a leaving group and X, Y, J, K, L, M, P, Q and $R^1$ to $R^6$ are as hereinbefore defined. Suitable leaving groups will be well known to those skilled in the art and include, for example, halo such as chloro and bromo; sulphonyloxy groups such as methanesulphonyloxy and toluene-p-sulphonyloxy; and alkoxy groups.

The reaction is conveniently carried out in the presence of a suitable inert solvent, for example a $C_{1-4}$ alkanol, such as isopropanol, a halogenated hydrocarbon, an ether, an aromatic hydrocarbon or a dipolar aprotic solvent such

as acetone at a non-extreme temperature, for example from 0 to 150°, suitably 10 to 100°C, preferably 50 to 100°C.

Optionally, the reaction is carried out in the presence of a base when Y = NH. Examples of suitable bases include an organic amine such as triethylamine, or an alkaline earth metal carbonate, hydride or hydroxide, such as sodium or potassium carbonate, hydride or hydroxide. When YH = OH or SH it is necessary to perform the reaction in the presence of a base, and in such a case the product is not obtained as the salt.

The compound of formula (I) in the case in which Y = $NR^b$ may be obtained from this process in the form of a salt with the acid HL, wherein L is as hereinbefore defined, or as the free base by treating the salt with a base as hereinbefore defined.

The preparation of compounds (II) and (III) is well known to those skilled in the art.

In addition to the above, one compound of formula (I) may be converted to another compound of formula (I) by chemical transformation of the appropriate substituent or substituents using appropriate chemical methods (see for example, J.March "Advanced Organic Chemistry", Edition III, Wiley Interscience, 1985).

For example a compound containing an alkyl or aryl mercapto group may be oxidised to the corresponding sulphinyl or sulphonyl compound by use of an organic peroxide (eg benzoyl peroxide) or suitable inorganic oxidant (eg OXONE ®)

A compound containing a nitro substituent may be reduced to the corresponding amino-compound, eg by use of hydrogen and an appropriate catalyst (if there are no other susceptible groups) or by use of Raney Nickel and hydrazine hydrate.

Amino or hydroxy substituents may be acylated by use of an acid chloride or an anhydride under appropriate conditions. Equally an acetate or amide group may be cleaved to the hydroxy or amino compound respectively by treatment with, for example, dilute aqueous base.

In addition reaction of an amino substituent with triphosgene and another amine (eg aqueous ammonia, dimethylamine) gives the urea substituted product.

An amino substituent may also be converted to a dimethylamino substituent by reaction with formic acid and sodium cyanoborohydride.

The present invention also provides compounds of formula (I) and pharmaceutically acceptable salts thereof (hereinafter identified as the 'active ingredients') for use in medical therapy, and particularly in the treatment of disorders mediated by aberrant protein tyrosine kinase activity such as human malignancies and the other disorders mentioned above. The compounds are especially useful for the treatment of disorders caused by aberrant c-erbB-2 activity such as breast, ovarian, non-small cell lung, pancreatic, gastric and colon cancers.

A further aspect of the invention provides a method of treatment of a human or animal subject suffering from a disorder mediated by aberrant protein tyrosine kinase activity which comprises administering to the human or animal subject an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

A further aspect of the present invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, in therapy.

A further aspect of the present invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, in the preparation of a medicament for the treatment of malignant tumours.

A further aspect of the present invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, in the preparation of a medicament for the treatment of atherosclerosis, resterosis or thrombosis.

Whilst it is possible for the compounds or salts of the present invention to be administered as the new chemical, it is preferred to present them in the form of a pharmaceutical formulation.

According to a further feature of the present invention we provide pharmaceutical formulations comprising at least one compound of the formula (I), or pharmaceutically acceptable salt(s) thereof, together with one or more pharmaceutically acceptable carriers, diluents or excipients.

Pharmaceutical formulations may be presented in unit dose forms containing a predetermined amount of active ingredient per unit dose. Such a unit may contain for example 0.5mg to 1g, preferably 5mg to 100mg of a compound of the formula (I) depending on the condition being treated, the route of administration and the age, weight and condition of the patient.

Pharmaceutical formulations may be adapted for administration by any appropriate route, for example by the oral (including buccal or sublingual), rectal, nasal, topical (including buccal, sublingual or transdermal), vaginal or parenteral (including subcutaneous, intramuscular, intravenous or intradermal) route. Such formulations may be prepared by any method known in the art of pharmacy, for example by bringing into association the active ingredient with the carrier(s) or excipient(s).

Pharmaceutical formulations adapted for oral administration may be presented as discrete units such as capsules or tablets; powders or granules; solutions or suspensions in aqueous or non-aqueous liquids; edible foams or whips; or oil-in-water liquid emulsions or water-in-oil liquid emulsions.

Pharmaceutical formulations adapted for transdermal administration may be presented as discrete patches intended to remain in intimate contact with the epidermis of the recipient for a prolonged period of time. For example, the active ingredient may be delivered from the patch by iontophoresis as generally described in Pharmaceutical Research, 3(6), 318 (1986).

Pharmaceutical formulations adapted for topical administration may be formulated as ointments, creams, suspensions, lotions, powders, solutions, pastes, gels, sprays, aerosols or oils.

For treatments of the eye or other external tissues, for example mouth and skin, the formulations are preferably applied as a topical ointment or cream. When formulated in an ointment, the active ingredient may be employed with either a paraffinic or a water-miscible ointment base. Alternatively, the active ingredient may be formulated in a cream with an oil-in-water cream base or a water-in-oil base.

Pharmaceutical formulations adapted for topical administrations to the eye include eye drops wherein the active ingredient is dissolved or suspended in a suitable carrier, especially an aqueous solvent.

Pharmaceutical formulations adapted for topical administration in the mouth include lozenges, pastilles and mouth washes.

Pharmaceutical formulations adapted for rectal administration may be presented as suppositories or as enemas.

Pharmaceutical formulations adapted for nasal administration wherein the carrier is a solid include a coarse powder having a particle size for example in the range 20 to 500 microns which is administered in the manner in which snuff is taken, i.e. by rapid inhalation through the nasal passage from a container of the powder held close up to the nose. Suitable formulations wherein the carrier is a liquid, for administration as a nasal spray or as nasal drops, include aqueous or oil solutions of the active ingredient.

Pharmaceutical formulations adapted for administration by inhalation include fine particle dusts or mists which may be generated by means of various types of metered dose pressurised aerosols, nebulizers or insufflators.

Pharmaceutical formulations adapted for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or spray formulations.

Pharmaceutical formulations adapted for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile

suspensions which may include suspending agents and thickening agents. The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets.

Preferred unit dosage formulations are those containing a daily dose or sub-dose, as herein above recited, or an appropriate fraction thereof, of an active ingredient.

It should be understood that in addition to the ingredients particularly mentioned above, the formulations may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavouring agents.

The compounds of the formula (I) and salts thereof have anticancer activity as demonstrated hereinafter by their inhibition of the protein tyrosine kinase c-erbB-2 enzyme. It has thus been established that compounds of the present invention are of use in medicine and, in particular in the treatment of certain human malignancies, for example breast, ovarian non-small cell lung, pancreatic, gastric and colon cancers. Accordingly, the present invention provides a method for the treatment of susceptible malignancies in an animal, e.g. a human, which comprises administering to the animal a therapeutically effective amount of a compound or salt of the present invention. In the alternative, there is also provided a compound or salt of the present invention for use in medicine and, in particular, for use in the treatment of cancers.

The present invention also provides the use of a compound of formula (I) or a salt thereof for the manufacture of a medicament for treatment of malignant tumours.

The animal requiring treatment with a compound or salt of the present invention is usually a mammal, such as a human being.

A therapeutically effective amount of a compound or salt of the present invention will depend upon a number of factors including, for example, the age and weight

of the animal, the precise condition requiring treatment and its severity, the nature of the formulation, and the route of administration, and will ultimately be at the discretion of the attendant physician or veterinarian. However, an effective amount of a compound of the present invention for the treatment of neoplastic growth, for example colon or breast carcinoma will generally be in the range of 0.1 to 100 mg/kg body weight of recipient (mammal) per day and more usually in the range of 1 to 10 mg/kg body weight per day. Thus, for a 70kg adult mammal, the actual amount per day would usually be from 70 to 700 mg and this amount may be given in a single dose per day or more usually in a number (such as two, three, four, five or six) of sub-doses per day such that the total daily dose is the same. An effective amount of a salt of the present invention may be determined as a proportion of the effective amount of the compound per se.

Certain embodiments of the present invention will now be illustrated by way of example only. The physical data given for the compounds exemplified is consistent with the assigned structure of those compounds.

IR spectra were recorded on a Perkin-Elmer 257 grating spectrophotometer or a Bruker FS66 spectrophotometer.
1H NMR spectra were obtained on a Bruker WM 360-NMR spectrophotometer at 360MHz, or on a Bruker AC250 spectrophotometer at 250MHz. J values are given in Hz.
Mass spectra were obtained on one of the following machines: Varian CH5D (EI), Kratos Concept (EI), Kratos Ms50 (FAB), VG Micromass Platform (electrospray positive or negative), HP5989A Engine (thermospray positive).
Analytical thin layer chromatography (tlc) was used to verify the purity of some intermediates which could not be isolated or which were too unstable for full characterisation, and to follow the progess of reactions. Unless otherwise stated, this was done using silica gel (Merck Silica Gel 60 F254).
Unless otherwise stated, column chromatography for the purification of some compounds used Merck Silica gel 60 (Art. 1.09385, 230-400 mesh), and the stated solvent system under pressure.
Petrol refers to petroleum ether, either the fraction boiling at 40-60°C, or at 60-80°C.
DMSO refers to dimethylsulphoxide.

Example 1

4-Chlorobenzo[g]quinazoline

3-Amino-2-naphthoic acid ( Aldrich, 2.0g, 10.7mmol) and formamidine acetate (4.0g, 38.4mmol) were reacted in glacial acetic acid (20ml) at reflux for 1 hour. The solution was allowed to cool, diluted with water and the product collected by filtration, washed with water, and dried at 60°C under vacuum to give 4-hydroxybenzo[*g*]quinazoline as a brown solid (1.7g, 81%). δH [$^2H_6$]-DMSO 12.00 (1H, b, OH), 8.84 (1H, s, 2-H), 8.29-8.05 (4H, m, 5-H, 6-H, 9-H, 10-H), 7.73-7.57 (2H, m, 7-H, 8-H).

4-Hydroxybenzo[*g*]quinazoline (0.5g, 2.5mmol) was reacted with phosphorous oxychloride (1.9ml, 20.7mmol) and triethylamine (1.0ml, 7.2mmol) at reflux under nitrogen for 2 hours. The reaction was concentrated at 70°C under vacuum, and then extracted four times with boiling 60/80 petrol. The combined extracts were evaporated to dryness, and the resulting solid was redissolved in boiling 60/80 petrol, filtered and the filtrate re-evaporated to give 4-chlorobenzo[*g*]quinazoline as yellow crystals (0.130g, 24%). δH [$^2H_6$]-DMSO 8.90 (1H, s, 2-H), 8.69 and 8.33 (2 x 1H, 2 x s, 5-H, 10-H), 8.26 and 8.16 (2 x 1H, 2 x d, 6-H, 9-H), 7.79-7.61 (2H, m, 7-H, 8-H).

4-(4-Benzyloxyanilino)benzo[g]quinazoline hydrochloride

4-Chlorobenzo[g]quinazoline (0.070g, 0.32mmol) and 4-benzyloxyaniline (0.070g, 0.35mmol) were heated to reflux in 2-propanol (3ml). After cooling the reaction was diluted with acetone and the precipitate collected by filtration and washed with acetone to give the product as yellow crystals (0.120g, 89%), m.p. 252-254° C; $C_{25}H_{19}N_3O.HCl.0.2H_2O$ requires C 71.92, H 4.93, N 10.07; found C 71.83, H 4.81, N 9.97; dH [$^2H_6$] -DMSO 12.05 (1H, br s, NH), 9.71 (1H, s, 2-H), 8.87 and 8.46 (2 x 1H, 2 x s, 5-H, 10-H), 8.30-8.16 (2H, m, 6-H, 9-H), 7.90-7.70 (4H, m, 7-H, 8-H, 2'-H, 6'-H), 7.57-7.31 (5H, m, 5xPhH), 7.17 (2H, d, 3'-H, 5'-H), 5.19 (2H, s, $OCH_2$); m/z 377 (M+); $\nu_{max}$ (KBr disc)/$cm^{-1}$ 2696, 2648, 1622, 1610.

Example 2

4-Chlorobenzothieno[3,2-d]pyrimidine

Methyl benzo[*b*]thiophene-2-carboxylate (prepared as described in *J. Org. Chem.*, Vol. 37, (21), pp 3224-6, 1972) (1.0g, 4.8mmol) and formamidine acetate

(2.0g, 19.2mmol) were reacted at reflux in glacial acetic acid (20ml) for 4 hours. After cooling the reaction was diluted with water, and the precipitate thus formed was collected by filtration. It was washed with water and acetone, and then dried at 60°C under vacuum to give 4-hydroxybenzothieno[3,2-*d*]pyrimidine as a white solid (0.56g, 57%); δH [$^2H_6$]-DMSO 12.79 (1H, b, OH), 8.34 (1H, s, 2-H), 8.29 and 8.16 (2 x 1H, 2 x d, 5-H, 8-H), 7.78- 7.57 (2H, m, 6-H, 7-H). 4-Hydroxybenzothieno[3,2-d]pyrimidine (0.5g, 2.5mmol) was reacted with phosphorous oxychloride (1.9ml, 20.7mmol) and triethylamine (1.0ml, 7.2mmol) at reflux under nitrogen for 2.5 hours. The reaction was concentrated at 70°C under vacuum and then extracted four times with boiling 60/80 petrol. The combined extracts were evaporated to dryness, and the resulting solid redissolved in boiling 60/80 petrol, filtered and the filtrate re-evaporated to give 4-Chlorobenzothieno[3,2-*d*]pyrimidine as a pale green solid (0.20g, 37%); δH [$^2H_6$]-DMSO 9.17 (1H, s, 2-H), 8.50 and 8.29 (2 x 1H, 2 x d, 5-H, 8-H), 7.86 and 7.71 (2 x 1H, 2 x t, 6-H, 7-H).

4-(4-Benzyloxyanilino)benzothieno[3,2-d]pyrimidine hydrochloride

4-Chlorobenzothieno[3,2-*d*]pyrimidine (0.100g, 0.45mmol) and 4-benzyloxyaniline (0.100g, 0.50mmol) were reacted at reflux for 3 hours in 2-propanol (4ml). After cooling, the reaction was filtered, and the precipitate was washed with 2-propanol and acetone to give the product as a yellow solid (0.080g, 42%), m.p. 201-203°C; $C_{23}H_{17}N_3OS.HCl$ requires C 65.78, H 4.32, N 10.01; found C 65.55, H 4.37, N 9.83. δH [$^2H_6$] -DMSO 10.77 (1H, b, NH), 8.84 (1H, s, 2-H), 8.66 and 8.21 (2 x 1H, 2 x d, 5-H, 8-H), 7.77 and 7.66 (2 x 1H, 2 x t, 6-H, 7-H), 7.59 (2H, d, 2'-H, 6'-H), 7.53-7.31 (5H, m, 5xPh-H), 7.11 (2H, d, 3'-H, 5'-H), 5.16 (2H, s, $OCH_2$); m/z 383 (M+); $\nu_{max}$ (KBr disc)/$cm^{-1}$ 2439, 1626, 1607.

Biological Data

Compounds of the present invention were tested for protein tyrosine kinase inhibitory activity in a substrate phosphorylation assay and a cell proliferation assay.

The substrate phosphorylation assay uses a baculovirus expressed, recombinant construct of the intracellular domain of c-erbB-2 that is constitutively active. The method measures the ability of the isolated enzyme to catalyse the transfer of $^{33}P$-labelled γ-phosphate from ATP onto tyrosine residues in a synthetic peptide.

The enzyme is incubated for 1 hour, at room temperature, with 100μM ATP, 10mM $MnCl_2$, 1mg/ml PolyGluAlaTyr (6:3:1) and test compound (diluted from a 5mM stock in DMSO, final DMSO concentration is 2%) in 40mM HEPES buffer, pH 7.4. The reaction is stopped by the addition of EDTA (final concentration 0.1M) and the peptide is then precipitated onto ion exchange filter paper and the incorporated radioactivity determined. The results are shown in the first column of Table 1 below as the $IC_{50}$ values in nM.

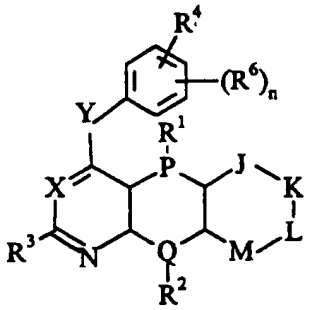
The cell proliferation assay uses an immortalised human breast epithelial cell line (HB4a) which has been transformed by over-expression of c-erbB-2. Growth of these cells in low serum is dependent upon the c-erbB-2 tyrosine kinase activity. The specificity of the effect of the test compounds on tyrosine kinase dependent growth over general toxicity is assessed by comparison to an HB4a cell line which has been transfected with ras. Cells are plated at 3000/well in 96-well plates in 0.1 ml medium and allowed to attach overnight. test compound is added in 0.1 ml medium, with a final concentration of 0.5% DMSO, and the plates incubated for 4 days at 37°C. The cells are then examined microscopically for evidence of morphological detransformation and cell mass is estimated by staining with methylene blue and measuring the absorbance at 620nm. The results are shown in the second and third columns of Table 1 below as the $IC_{50}$ values in nM.

Table 1

| Compound of Example | erbB-2 Substrate Phosphorylation | HB4a erbB-2 Cell Proliferation | HB4a ras Cell Proliferation |
|---|---|---|---|
| 1 | 1200 | 3500 | 10000 |

Claims

1. A compound of formula (I):



(I

or a pharmaceutically acceptable salt thereof, wherein:

J, K, L and M form a saturated or unsaturated fused ring which is optionally substituted and in which:

(i) each of J, K, L and M represent carbon atoms that may be independently replaced by N, O or S; or

(ii) any two contiguous positions in J, K, L and M taken together represent a single atom C, N, O or S with at least one of the remaining atoms being carbon and the other being selected from carbon, N, O or S; or

(iii) any two contiguous positions in J, K , L and M taken together represent a N atom with the remaining atoms also being N;

so that when the fused 5 or 6-membered ring represented by J, K, L and M bears one or two optional substituents in order to satisfy the valency requirements of the atoms in the fused ring and:

(i) when the ring atom is carbon, the substituents are independently selected from the group comprising: amino, cyano, halogen, hydroxy, $C_{1-4}$ alkyl, $C_{1-4}$ alkoxy, $C_{1-4}$alkylthio, $C_{1-4}$ alkylsulphinyl, $C_{1-4}$ alkylamino, or

(ii) when there are two adjacent carbon atoms in the fused ring, two substituents together form an optionally substituted methylenedioxy or ethylenedioxy group, or

(iii) when the ring atom is nitrogen, the substituents are independently selected from the group comprising: $C_{1-4}$ alkyl, amino $C_{2-4}$ alkyl, hydroxy $C_{2-4}$ alkyl and $C_{1-4}$ alkoxy $C_{2-4}$ alkyl;

subject to the provisos in (i) and (ii) above that the skeleton of the fused heterocyclic ring does not contain more than two atoms selected from O and S, and where the fused ring contains two such atoms said atoms do not occupy adjacent positions in the fused ring;

P and Q are carbon atoms in an aromatic ring which may be independently replaced to form an aromatic or non-aromatic ring by O, N, S, or a bond; or one of P and Q is C=C or C=N and the other a bond;

X is N or CH;

Y is a group $W(CH_2)$, $(CH_2)W$, or W, in which W is O, $S(O)_m$ wherein m is 0, 1 or 2, or $NR^a$ wherein $R^a$ is hydrogen or a $C_{1-8}$ alkyl group;

$R^1$ and $R^2$ are independently selected as appropriate to the nature of P and Q from the group comprising; not present, a lone pair of electrons, amino, hydrogen, halogen, hydroxy, nitro, carboxy, trifluoromethyl, trifluoromethoxy, carbamoyl, ureido, $C_{1-8}$ alkyl, $C_{1-8}$ alkoxy, $C_{3-8}$ cycloalkoxy, $C_{4-8}$ alkylcycloalkoxy, $C_{1-8}$ alkoxycarbonyl, N-$C_{1-4}$ alkylcarbamoyl, N,N-di-[$C_{1-4}$ alkyl]carbamoyl, hydroxyamino, $C_{1-4}$ alkoxyamino, $C_{2-4}$ alkanoyloxyamino, $C_{1-4}$ alkylamino, di[$C_{1-4}$ alkyl]amino, $C_{1-8}$ alkylthio, arylthio, $C_{1-4}$ alkylsulphinyl, arylsulphinyl, $C_{1-4}$ alkylsulphonyl, arylsulphonyl, halogeno-$C_{1-4}$ alkyl, and hydroxy-$C_{1-4}$ alkyl;

$R^3$ is selected from the group comprising; hydrogen, halogen, trifluoromethyl, $C_{1-4}$ alkyl and $C_{1-4}$ alkoxy;

$R^4$ is a group $ZR^5$ wherein Z is joined to $R^5$ through a $(CH_2)p$ group in which p is 0, 1 or 2 and Z represents a group $V(CH_2)$, $V(CF_2)$, $(CH_2)V$, $(CF_2)V$, or V in which V is a hydrocarbyl group containing 0,1 or 2 carbon atoms, carbonyl, CH(OH), sulphonamide, amide, O, $S(O)_m$ or $NR^b$ where $R^b$ is hydrogen or $R^b$ is $C_{1-4}$ alkyl;

or $R^4$ is a group $ZR^5$ in which Z is $NR^b$, and $NR^b$ and $R^5$ together form an optionally substituted 5, 6, 7, 8, 9 or 10-membered heterocyclic moiety;

$R^5$ is an optionally substituted 5, 6, 7, 8, 9 or 10-membered carbocyclic or heterocyclic moiety, or an optionally substituted $C_{3-6}$ cycloalkyl provided p is not zero; and

each $R^6$ is independently selected from the group comprising; hydrogen, hydroxy, halogen, $C_{1-4}$ alkyl, $C_{1-4}$ alkoxy, $C_{1-4}$ alkylamino, di-[$C_{1-4}$ alkyl]amino, $C_{1-4}$ alkylthio, $C_{1-4}$ alkylsulphinyl, $C_{1-4}$ alkylsulphonyl, $C_{1-4}$ alkylcarbonyl, $C_{1-4}$ alkylcarbamoyl, di-[$C_{1-4}$ alkyl] carbamoyl, carbamyl, $C_{1-4}$ alkoxycarbonyl, cyano, nitro and trifluoromethyl, and n is 1,2 or 3.

2. A compound as claimed in claim 1, wherein P and Q are both C atoms.

3. A compound as claimed in claim 1, wherein one of P and Q is a N, O or S atom, with the other being a bond.

4. A compound as claimed in any one of claims 1 to 3, wherein J, K, L and M are all C atoms, optionally with J, K , L and M forming a further aromatic ring.

5. A compound as claimed in any preceding claim, wherein:
$R^1$ and $R^2$ are independently selected from the group comprising: amino, hydrogen, halogen, hydroxy, nitro, $C_{1-8}$ alkyl, $C_{1-8}$ alkoxy, $C_{1-8}$ alkylthio, $C_{1-8}$ alkylsulphinyl, $C_{1-8}$ alkylsulphonyl, and $C_{1-4}$ alkylamino;
$R^3$ is hydrogen, $C_{1-4}$ alkyl, $C_{1-4}$ alkoxy or halogen;
$R^5$ is an optionally substituted 5, 6, 7, 8, 9 or 10 membered-carbocyclic or heterocyclic moiety;
$R^6$ is hydrogen, hydroxy, halogen, $C_{1-4}$ alkyl, $C_{1-4}$ alkoxy, di-[$C_{1-4}$ alkyl]amino, nitro or trifluoromethyl; and
Z is oxygen, S or $NR^b$ wherein $R^b$ is hydrogen, or $C_{1-4}$ alkyl.

6. A compound as claimed in any preceding claim, wherein $R^1$ and $R^2$ are independently selected from the group comprising: hydroxy, halogen, amino, $C_{1-4}$ alkyl such as methyl, and $C_{1-4}$ alkoxy such as methoxy;
$R^3$ is hydrogen;

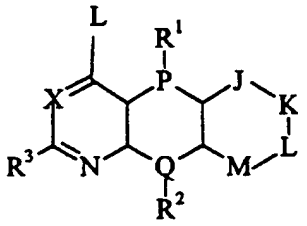
$R^4$ is benzyl, phenoxy or benzyloxy;
X is N and Y is $NR^b$, $NR^b(CH_2)$, or $(CH_2)NR^b$; or X is CH and Y is O or $S(O)_m$, wherein m, $R^a$ and $R^b$ are as defined in claim 1; and
$R^6$ is hydrogen, halogen or methyl.

7. A compound as claimed in claim 1 selected from the group comprising:
4-(4-Benzyloxyanilino)benzo[g]quinazoline hydrochloride and
4-(4-Benzyloxyanilino)benzothieno[3,2-d]pyrimidine hydrochloride,
and pharmaceutically acceptable salts thereof.

8. A pharmaceutical formulation comprising one or more compounds of formula (I), or a pharmaceutically acceptable salt thereof, together with one or more pharmaceutically acceptable carriers, diluents or excipients.

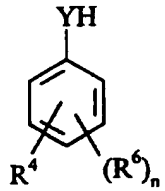
9. A pharmaceutical formulation as claimed in claim 8 in unit dosage form and containing a compound of formula (I) or a pharmaceutically acceptable salt thereof in an amount from 70 to 700 mg.

10. A process for the preparation of a compound of formula (I), or a pharmaceutically acceptable salt thereof, which process comprises the reaction of a compound of the formula (II).




(II)

with a compound of the formula III :




(III)

wherein L is a leaving group and X, Y, J, K, L, M, P, Q and $R^1$ to $R^6$ are as defined in claim 1.

11. A process as claimed in claim 10, wherein the process also includes the step of converting a compound of formula (I) into another compound of formula (I).

12. A compound of formula (I), or a pharmaceutically acceptable salt thereof, for use in therapy.

13. Use of a compound of formula (I) or a pharmaceutically acceptable salt thereof in the preparation of a medicament for the treatment of a disorder mediated by aberrant tyrosine kinase activity.

14. Use of a compound of formula (I) or a pharmaceutically acceptable salt thereof in the preparation of a medicament for the treatment of malignant tumours.

15. Use of a compound of formula (I) or a pharmaceutically acceptable salt thereof in the preparation of a medicament for the treatment of atherosclerosis, restenosis or thrombosis.

16. A method of treatment of a human or animal subject suffering from a disorder mediated by aberrant tyrosine kinase activity which comprises administering to the human or animal subject an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

# INTERNATIONAL SEARCH REPORT

Interr al Application No
PCT/EP 96/04396

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D239/70 C07D495/04 C07D491/04 A61K31/505

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| A | EP,A,0 635 507 (ZENECA) 25 January 1995<br>cited in the application<br>see claims; examples 7,8 | 1-3,<br>10-15 |
| A | WO,A,95 19970 (WARNER-LAMBERT) 27 July 1995<br>cited in the application<br>see the whole document | 1,3,4,<br>10-15 |
| A | US,A,3 755 583 (G. DE ANGELIS) 28 August 1973<br>see column 1 - column 18 | 1,3,<br>10-15 |

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

2

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 23 January 1997 | - 4 -02- 1997 |

| Name and mailing address of the ISA | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,<br>Fax: (+31-70) 340-3016 | Francois, J |

Form PCT/ISA/210 (second sheet) (July 1992)

## INTERNATIONAL SEARCH REPORT

I: ational application No.
PCT/EP 96/04396

**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claim 16 is directed to a method of treatment of the human body, the search has been carried out and based on the attributed effects of the compounds. (Rule 39.1 (iv)PCT)

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern al Application No
PCT/EP 96/04396

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